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## VERSATILE CATALYTIC TRANSFER HYDROGENATIONS IN ORGANIC SYNTHESIS

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### Key words:

Hydrogenation, Catalytic Transfer Hydrogenation, Hydrogenolysis, Beta Lactam, Bond Cleavage, Ammonium Formate, Hydrazine, Palladium-Carbon, Dehalogenation, and Reduction

### Abstract:

Catalytic transfer hydrogenation reactions are extremely useful in organic synthesis. We have investigated numerous reactions with ammonium formate (and other hydrogen gas donor) and 10% Pd/C successfully without using hydrogen gas. The reactions are very fast and produced products with high yields. Reduction of unsaturated groups, hydrogenolysis, reductive bond cleavage, allylic deacetoxylation, and dehalogenation are conducted using this method. In some instances, useful selectivity of reactions is observed. Most of the reactions are investigated with  $\beta$ -lactams as the substrates.

### Introduction:

Catalytic hydrogenation is an important reaction in chemistry. In general, this reaction is conducted with different percentages of Pd/C (10% or 5%) and hydrogen gas under vacuum using an organic solvent (ethanol, tetrahydrofuran, ethylene glycol, etc.). The most important limitation of this method is that hydrogen gas is flammable and it becomes more fire-sensitive in the presence of Pd/C. Moreover, it is necessary to remove excess hydrogen gas from the reaction mixture after completion of the reaction to avoid fire hazards. As an alternative, catalytic transfer hydrogenation method is introduced to accomplish same goal. In this method, a donor generates hydrogen gas in the presence of Pd/C and a solvent at relatively high temperature. Ammonium formate, sodium formate, Raney nickel, formic acid, hydrazine, cyclohexadiene, phosphinic acid, cyclohexene and sodium hypophosphite are commonly used for this purpose as hydrogen donor. No low pressure vacuum system is required in catalytic transfer hydrogenation. The amount of the donor used for this reaction is very important. It is found that three equivalents of donor (ammonium formate, sodium formate, and cyclohexadiene) produced products when the molecule has one reducible group. It is necessary to use higher amount of the hydrogen donor for complete reaction if the molecule has multiple reducible groups. Higher amount of catalysts may also produce mixture of products. The best results are

obtained when 10 mol% catalyst are used. The amount of catalyst needed for a reaction is calculated from the structure of the starting compound and the number of reducible groups present in it. Using this method, numerous reactions with  $\beta$ -lactams (reduction of unsaturated groups, hydrogenolysis, reductive bond cleavage, allylic deacetoxylation, and dehalogenation) are conducted and useful selectivity of product formation is observed. This method is extremely rapid, economical and much more convenient than standard hydrogenation reaction.

## Results and Discussions:

### Hydrogenolysis of Benzyl Ether group in Optically Active $\beta$ -Lactams:

The benzyl ether group at C-3 position of several  $\beta$ -lactam rings that have protected sugar units at C-4 position was removed with ammonium formate and 10% Pd-C in ethanol at approximately 50°C [1]. This reaction produced optically active hydroxy  $\beta$ -lactams without loss of optical purity. To remove this type of benzyl ether group with hydrogen gas and 10% Pd/C under vacuum at room temperature, more than 8 hours was necessary. The yield of the hydroxy  $\beta$ -lactams was more than 90%. A benzyl group connected to the nitrogen of the  $\beta$ -lactam ring remained unaffected even after prolonged exposure of the reaction mixture under the reaction conditions. This type of chemoselectivity is very crucial for the total synthesis of optically active natural and non-natural products.

### Hydrogenolysis of the Benzyl Amine in Optically Active Amines:

Optically active N-benzyl amines were removed to primary amines in the presence of ammonium formate and 10% Pd-C in ethanol [2]. This reaction was also performed successfully with hydrazine hydrate and sodium formate as the donor. This method was used as one of the key steps for the total synthesis of polyhydroxy aminoacids. Protected ketal group remained unaffected and the reaction produced products without altering the absolute stereochemistry of any of the intermediates and final products.

### Hydrogenolysis of the N-C-4 Bond Cleavage in Racemic $\beta$ -Lactams:

The N-C-4 bond was cleaved in C-4-aromatic ring-substituted  $\beta$ -lactams with ammonium formate and 10% Pd/C. This reaction produced amides in excellent yields [3]. The compounds without an aromatic group at C-4 failed to produce amide through scission of the N-C-4 bond in  $\beta$ -lactams. It was possible to perform selective hydrogenolysis in  $\beta$ -lactam chemistry by choosing the substrates carefully.

### Hydrogenation of the Alkene Group in Racemic $\beta$ -Lactams:

The unsaturated alkene group in  $\beta$ -lactams was hydrogenated when Raney nickel was used as the catalyst and ammonium formate as the donor [3]. Thus, it was possible to control the reaction at the reduction stage. The use of ammonium formate and Pd/C was able to hydrogenate the alkene group as well as cleave the ring system. Thus 3-alkylated  $\beta$ -lactam was easily accessible by this method. Direct synthesis of 3-alkyl substituted  $\beta$ -lactams by acid chloride-imine cycloaddition reaction was difficult. Moreover, the stereochemistry of the direct cycloaddition produced *cis*  $\beta$ -lactams where alkenyl  $\beta$ -lactam produced *cis* or *trans*  $\beta$ -lactams depending upon the nature of the compounds used for catalytic transfer hydrogenation method [4].

### Hydrogenation of the Alkyne Group in Racemic $\beta$ -Lactams:

Alkyne group was hydrogenated to alkane with ammonium formate and Raney nickel in  $\beta$ -lactams in the absence of an aromatic group at C-4 position of the ring [5]. However, ammonium formate and 10% Pd/C was able to saturate the alkyne to alkane with the cleavage of the N-C-4 bond, if an

aromatic ring is present at the C-4 position of the ring. The alkyne group in  $\beta$ -lactams was hydrogenated to alkane regardless of its position at N-1, C-3 or C-4.

#### **Hydrogenolysis of the Benzyl Ether and N-C4 Bond Cleavage in Racemic $\beta$ -Lactams:**

Ammonium formate and 10% Pd/C was suitable to conduct hydrogenolysis of the benzyl ether group and cleave the N-C-4 bond in  $\beta$ -lactams very efficiently [3]. If the aromatic group is two carbons away from the C-4 position, no cleavage of the N-C-4 bond was observed indicating the importance of the location of the aromatic group in the  $\beta$ -lactam ring. This observation suggested that N-C-4 bond cleavage is only possible if there is an aromatic group directly connected to the C-4 position of the ring.

#### **Reduction of the alkene group in Sugar Connected to Optically Active $\beta$ -Lactams:**

The reduction of alkene group in sugar connected to an optically active without an aromatic group at C-4 in  $\beta$ -lactams proceeded smoothly [6]. A same reaction with an aromatic group at C-4 of  $\beta$ -lactam caused reduction of the alkene, N-C-4 bond cleavage and deacetoxylation of the allylic acetoxy group provided an excess amount of Pd/C and ammonium formate was used in this reaction [6]. However, it was difficult to control these reactions since it appears all these reactions take place simultaneously.

#### **Reduction of Optically Active Azides in $\beta$ -Lactams:**

Azido group in  $\beta$ -lactams were reduced to amines by catalytic transfer hydrogenation with ammonium formate and 10% Pd/C. No inversion of stereochemistry of the  $\beta$ -lactam ring was occurred [7].

#### **Reduction of the Aromatic Mononitro and Aromatic Dinitro Compounds to the corresponding Amines:**

Reduction of the aromatic nitro groups to aromatic amines is an important objective. Monocyclic to polycyclic nitro compounds were reduced to the amines with 10% Pd-C and hydrazine hydrate [8]. Ammonium formate was also used with success. Similarly, many aromatic dinitro compounds were reduced to aromatic diamino compounds with these reagents combination. The use of many of these amines was published in our endeavor to develop novel anticancer agents [8].

#### **Hydrogenolysis of the Hydrazones to Amines:**

Hydrazones of ketones were reduced to amine by ammonium formate and 10% Pd/C. The amine was characterized following an acetylation experiment [3, 9].

#### **Reduction of Imines to Amino Derivatives:**

Schiff bases were reduced to secondary amines very effectively by catalytic transfer hydrogenation with ammonium formate and 10%Pd/C in ethanol. Optically active and racemic imines were used for successful reduction [9].

#### **Dehalogenation of Aromatic Compounds:**

Catalytic transfer hydrogenation method was applied successfully to dehalogenate iodo, bromo and chloro compounds. For example, monocyclic to tricyclic aromatic halogen containing compounds were reduced to their corresponding hydrocarbons by ammonium formate and 10% Pd/C [3b]. It was interesting to observe formation of approximately 10% dimeric product during this reduction. Optically active 3-iodo  $\beta$ -lactam was reduced to 3-unsubstituted  $\beta$ -lactam following this method.

### Microwave-Induced Methods:

The reactions described above were performed under classical method using ethanol as the solvent. The time for the completion of these reactions varies from 10 min-30 minutes at 50-60<sup>0</sup>C. All these procedure were conducted following microwave-induced reactions and identical products were obtained within 1-5 min. The reactions in microwave were performed using ethylene glycol as the solvent [10]. It was postulated that metals are very hazards in microwave-induced reactions. Therefore, our studies in this area with microwave were investigated with careful attention. The flammable nature of 10% Pd/C in presence of liberated hydrogen gas from the donor at relatively high temperature was minimized by keeping the metal under wet condition with ethylene glycol. In some instances, the reaction can be stopped at the specific reduction stage using 5% Pd/C and by not irradiating the reactants for an extended time. A few trial experiments were conducted to know precisely the time required for a specific reaction, although these reactions are very fast and sensitive. Scientists should be careful in conducting catalytic transfer hydrogenation reaction in microwave or by classical method as this reaction is fire-sensitive. These reactions should be conducted in well-ventilated hood by taking care of all safety protection (eye glass, gloves, laboratory coat and fire protector). It is recommended to perform this reaction taking help from a laboratory colleague.

### Conclusions:

Catalytic transfer hydrogenation has become a powerful method in the synthesis of diverse organic compounds. A variety of reactions with  $\beta$ -lactams to bioactive products and other important molecules are demonstrated [11, 12]. These reactions are rapid and isolation of products is easy. Different types of products are synthesized by choosing the substrates carefully. Based upon the diversity of this method, it should find numerous applications in chemistry. We are pursuing further studies in these areas.

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